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Chromosome Abnormalities in Congenital Heart Disease

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Refinements in cytogenetic techniques have promoted progress in understanding the role that chromosome abnormalities play in the cause of congenital heart disease. To determine if mutations at specific loci cause congenital heart disease, irrespective of the presence of other defects, and to estimate the prevalence of chromosome abnormalities in selected conotruncal cardiac defects, we reviewed retrospectively cytogenetic and clinical databases at St. Louis Children's Hospital. Patients with known 7q11.23 deletion (Williams syndrome), Ullrich-Turner syndrome (UTS), and most autosomal trisomies were excluded from this analysis. Two groups of patients were studied. Over a 6.5-year period, 57 patients with chromosomal abnormalities and congenital heart disease were identified. Of these, 37 had 22q11 deletions; 5 had abnormalities of 8p; and 15 had several other chromosome abnormalities. The prevalence of chromosome abnormalities in selected conotruncal or aortic arch defects was estimated by analysis of a subgroup of patients from a recent 22-month period. Chromosome abnormalities were present in 12% of patients with tetralogy of Fallot, 26% in tetralogy of Fallot/pulmonary atresia, 44% in interrupted aortic arch, 12% in truncus arteriosus, 5% in double outlet right ventricle, and 60% in absent pulmonary valve. We conclude that chromosome analysis should be considered in patients with certain cardiac defects. Specifically, fluorescent in situ hybridization (FISH) analysis of 22q11 is indicated in patients with conotruncal defects or interrupted aortic arch. High resolution analysis should include careful evaluation of the 8p region in patients with either conotruncal or endocardial cushion defects. Am. J. Med. Genet. 70:292–298, 1997.

KEY WORDS: 22q deletion; conotruncal congenital heart defects; 8p deletion

INTRODUCTION

Recent clinical and basic work has shown the importance of genetic factors in the cause of congenital heart defects [Payne et al., 1995]. Chromosome abnormalities are associated with 8–13% of congenital heart disease; however, these data were generated before fluorescent in situ hybridization (FISH) analysis was commonly used [Nora et al., 1991; Ferencz et al., 1989]. In the past, a chromosome cause of cardiac defects was investigated only if other organ system involvement or syndromic anomalies were identified [Nora et al., 1991]. The improved resolution of cytogenetic analysis and the addition of molecular techniques have allowed advancements in localization and detection of loci critical for cardiac development. For example, delineation of the del 22(q11) (also known as CATCH-22) syndrome was initiated by the identification of chromosome 22q11 monosomy in patients with DiGeorge syndrome [de la Chapelle et al., 1981; Greenberg et al., 1988; Wilson et al., 1993].

Because of the increasing use of cytogenetic techniques in the evaluation of patients with congenital heart disease at St. Louis Children's Hospital, we reviewed our recent experience with chromosome abnormalities and congenital heart disease to address four questions: (1) Is the incidence of chromosome abnormalities in conotruncal defects higher than that estimated by population-based analysis [Ferencz et al., 1989]? (2) Are there specific chromosome regions that should be closely scrutinized as part of the cytogenetic evaluation of patients with congenital heart disease? (3) Do noncardiac manifestations predict 22q11 deletions in patients with congenital heart defects? (4) Do 22q11 deletions occur in patients with apparently isolated cardiac defects?

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MATERIALS AND METHODS

The St. Louis Children's Hospital cytogenetic laboratory database was reviewed retrospectively from January 1989 through June 1995 to identify patients with congenital heart disease and chromosome abnormalities. Samples for chromosome analysis had been sent at the discretion of the attending physicians. Abnormalities detected by routine cytogenetic and FISH analysis were included. Patients with the following chromosome abnormalities were excluded from analysis: trisomy 13, trisomy 18, trisomy 21 patients with atrioventricular canal defects or isolated ventricular septal defects, 45, X and related X chromosome abnormalities, and 7q11.23 deletions (elastin). One patient had a chromosome analysis at another institution.

The prevalence of chromosome abnormalities in selected cardiac defects was determined in the interval since FISH analysis for del 22(q11) was introduced in August 1993. Databases from the outpatient cardiology service, cardiac surgery service, echocardiography, and catheterization laboratories were searched from this interval (August 1993 through June 1995) to identify the number of patients encountered at St. Louis Children's Hospital with the following defects: tetralogy of Fallot including pulmonary atresia, absent pulmonary valve, interrupted aortic arch, truncus arteriosus, and double outlet right ventricle. During this interval, all samples submitted to the cytogenetic laboratory from patients with these selected cardiac defects underwent FISH testing with the N25 probe.

Inpatient and outpatient records were reviewed to obtain clinical data. The anatomic diagnosis was verified from operative findings at cardiac surgery when applicable. In del 22(q11) syndrome patients, minor anomalies were scored as present if they were noted in the chart before the 22q11 deletion was identified. Patients were not routinely examined by a geneticist before chromosome studies were ordered. The presence of developmental delay was not assessed in patients less than 6 months old at the time of chart review or death.

Standard cytogenetic analysis was performed after ethidium bromide exposure of cultured skin fibroblasts or blood lymphocytes stimulated by either phytohemagglutinin or pokeweed mitogen. FISH testing was performed with the N25 cosmid probe (D22S75) for the deletion region in 22q11.2, and the control pH17 probe (D22S39) which tags the 22q13.3 band (Oncor, Inc., Gaithersberg, MD). Scoring and validation with these probes in our laboratory were described previously [Johnson et al., 1995a]. Karyotypes were described in accordance with the International System for Human Cytogenetic Nomenclature [Mitelman, 1995].

RS/1, version 4.4.1 (Bolt, Beranek & Newman, Inc., Cambridge, MA), was used for statistical calculations. Analysis of frequencies is performed with the chi-square test or Fisher's exact test.

RESULTS

Chromosome Abnormalities

During the entire study period (January 1989 to June 1995), 57 patients with congenital heart defects and chromosome abnormalities met the inclusion criteria. Deletion in 22q11 accounted for 37 of these patients. FISH analysis identified all 37 of the 22q11 deletions, whereas only 7 were detected with routine cytogenetic analysis. Seven patients with the 22q11 deletion, 6 with absent pulmonary valve, and one with anomalous origin of the right pulmonary artery from the aorta were reported previously [Johnson et al., 1995a, b].

Patients with chromosome disorders other than the del 22(q11) syndrome are listed in Table I. The small isodicentric marker chromosome 15 of patient 7 predominately contained heterochromatin. The unaffected mother of patient 7 was mosaic for this chromosome 15 marker. Patients 11 and 12 have cardiac defects that are uncommon for trisomy 21 but have typical noncardiac signs of Down syndrome. The marker chromosome of patient 13 was the size of 18p and mostly C-band negative. The unaffected father of patient 15 and the unaffected mother of patient 19 carried the same chromosome abnormalities as their children. Cytogenetic analysis was normal in both parents of patients 3,6,8,9, and 18.

Minor anomalies and developmental abnormalities characterized the 5 patients (1 to 5 in Table I) with an abnormality of the short arm of chromosome 8. Patient 1 had a ridged metopic suture, bitemporal narrowing, upslanted palpebral fissures, ptosis, apparently low-set ears, and micrognathia. Patient 2 had occipital plagiocephaly, prominent eyes, posteriorly angulated ears with flattened helix, broad neck, and tapered fingers. Formal developmental testing in patient 3 showed mild mental retardation with an I.Q. of 70 at age 10 years and physical examination was notable for left esotropia and micrognathia. Patient 4 had a narrow forehead, downslanted palpebral fissures, apparently low-set and posteriorly angulated ears, excess nuchal skin, and brachydactyly. Motor and speech delay were noted at age 21 months. Patient 5 had mild microcephaly, bitemporal narrowing, upslanted palpebral fissures, prominent nasal bridge, and micrognathia. Developmental evaluation at 3.5 years showed speech delay and hyperactivity.

Clinical findings of the 30 patients (10 males and 20 females) with FISH confirmed deletion in 22q11 (excluding the previously reported patients) are shown in Table II. Deletions in this region were also detected by standard cytogenetic analysis in 6 of the 30 patients. Absence of the thymus in the mediastinum at the time of surgery was documented in 7 of these patients, 5 with interrupted aortic arch and 2 with ventricular septal defects. Seven of 11 deleted patients with lymphocyte subpopulation quantification had low CD4 counts. Among the 7 patients with low CD4 counts, lymphocyte testing was performed at less than one year of age in all but one patient.

Seven sets of parents, 4 mothers and one father, of patients in Table II were not deleted by FISH analysis. The mother of patient 15 has a 22q11 deletion. She has no heart disease but does have velopharyngeal incompetence. The father of patient 19 has a 22q11 deletion. He has micrognathia and abnormal T-cell subpopulations but is otherwise phenotypically normal. An older

TABLE I. Chromosome Defects Other Than del(22)(q11.21q11.23)*

	Chromosome abnormality	Cardiac defect	Other	Developmental delay	Syndromal
1	46,XX,del(8)(p21.1p22)	AVC	Lebers amaurosis	Yes	Yes
2	46,XX,inv dup(8)(p23p12)	TA,LSVC	Agenesis of corpus callosum, vertebral anomalies, duplicated right renal system	?	Yes
3	46,XX,del(8)(p23.1)	TOF, AVC	Scoliosis	Yes	No
4	46,XY,add(8)(p23;?)	MA, DORV	—	Yes	Yes
5	46,XY,del(8)(23.1)	ASD, VSD	—	Yes	Yes
6	45,XX,−15,der(22)t(15;22)(q13;qter)	TAPVR, ASD	Hypotonia	Yes	Yes
7	47,XY,−13,+der(13)t(13;15)(p10;p10),+idic(15)(q10)	Dbl AA, Coart	Submucous cleft palate	Yes	Yes
8	46,XX,add(14)t(14;?)(p13;?)	PDA, PPS	—	No	No
9	46,XY,dup(4)(q31q34)	TOF	Seizures, cerebral atrophy	Yes	Yes
10	46,XX,?dup(22)(q12.1q13.1)	TOF	Cleft lip, hip dysplasia	Yes	Yes
11	47,XX,+21	TOF	—	Yes	Yes
12	47,XY,+21	TOF,PDA	—	Yes	Yes
13	47,XY,+mar	TOF,PDA	—	No	No
14	47,XXX	ASD	Strabismus, central hypotonia	Yes	Yes
15	46,XX,t(8;12)(q22.1;q21.1)	TGV,VSD	—	No	No
16	46,XX,t(2,6)(q23;q22)	AVC	—	No	No
17	46,XY,r(21)(p11q12)	IAA/B,APW	Club feet, inguinal hernias, dislocated hip	?	Yes
18	46,XX,add(4)(q31.3)	TAPVR,RAA	Club foot, tracheomalacia	Yes	Yes
19	46,XX,−13,+der(13)	HLH,ARSA,TAPVR	—	?	No
20	45,X/46,X,idic(Yqter-p11::p11-qter)	HLH	—	?	No

*APW, aortopulmonary window; ARSA, aberrant right subclavian artery; ASD, secundum atrial septal defect; AVC, atrioventricular canal; Coart, coarctation of the aorta; Dbl AA, double lumen aortic arch; DORV, double outlet right ventricle; HLH, hypoplastic left heart; IAA/B, interrupted aortic arch, type B; LSVC, left superior vena cava; MA, mitral atresia; PDA, patent ductus arteriosus; PPS, peripheral pulmonary artery stenosis; RAA, right aortic arch; TA, truncus arteriosus; TAPVR, total anomalous pulmonary venous return; TGV, transposition great vessels; TOF, tetralogy of Fallot; VSD, ventricular septal defect.

sib of patient 19 died neonatally with an interrupted aortic arch, minor anomalies, absent thymus and hypocalcemia. FISH and cytogenetic studies are normal in the paternal grandparents of patient 19. If these results are combined with our previous reports [Johnson et al., 1995a,b], parental deletions were present in 4 of 11 families with completed parental evaluations. Parental chromosomes have not been submitted in 18 of these 37 families.

Prevalence of Chromosome Abnormalities in Selected Cardiac Defects

Prevalence data were generated for selected conotruncal and aortic arch defects (absent pulmonary valve, tetralogy of Fallot, tetralogy of Fallot/pulmonary atresia, interrupted aortic arch, truncus arteriosus, and double outlet right ventricle) during the period since the introduction of FISH testing (August 1993 to June 1995). Table III shows the total number of patients with these defects encountered by the cardiology (inpatient and outpatient) or cardiac surgery services at St. Louis Children's Hospital during this period, the subset of these patients with FISH testing for del 22(q11) and/or routine cytogenetic testing, and the frequency of known chromosome abnormalities in these lesions. Patients with additional major cardiac defects are included in this analysis. Six of the 21 patients with double outlet right ventricle had other major cardiac defects including mitral atresia, hypoplastic left heart, atrioventricular canal, anomalous pulmonary venous return, and dextrocardia. Other combinations included tetralogy of Fallot with atrioventricular canal (patient 3 in Table I), interrupted aortic arch with aortopulmonary window (patient 17 in Table I), and interrupted aortic arch with truncus arteriosus (normal cytogenetic and FISH studies). Patients in Table III with only routine cytogenetic analysis were seen during the study period but had samples submitted from a previous visit before FISH testing was available.

Frequency of Clinical Findings in del 22(q11) Syndrome

To test the hypothesis that extracardiac manifestations predict the 22q11 deletion in patients with cardiac defects, we reviewed clinical and cytogenetic databases from the August 1993 to June 1995 study period to identify patients with FISH testing and the following cardiac defects: absent pulmonary valve, tetralogy of Fallot, tetralogy of Fallot/pulmonary atresia, interrupted aortic arch, truncus arteriosus, and anomalous origin of the pulmonary artery from the aorta. Seventy patients with these defects had cytogenetic testing and FISH analysis for the 22q11 deletion. Patients with other chromosome abnormalities were excluded from this analysis. Because cytogenetic samples from patients with isolated ventricular septal defects were not routinely tested by FISH analysis, these patients were also excluded. Table IV compares the frequency of clinical findings in these 70 patients according to the presence (n = 33) or absence (n = 37) of the 22q11 deletion. Minor anomalies, hypocalcemia, and abnormalities of the palate are predictive of 22q11 deletions in patients with conotruncal and aortic arch defects. However, in 9 patients minor anomalies were

TABLE II. Patients With del(22)(q11.21q11.23)*

	Cardiac defect	Other cardiac abnormalities	Other congenital defects	Developmental delay	Minor anomalies	Age at FISH (years)
1	TOF	RAA	TE fistula	Yes	Yes	0.8
2	TOF	ALSA,RAA	—	No	Yes	1.0
3	TOF	ARSA,NPA	Cleft palate,VI	No	Yes	12.0
4	TOF	RAA	Tracheomalacia	Yes	No	0.3
5	TOF	BPV,RAA	—	No	No	1.8
6	TOF	—	Umbilical hernia, branchial cyst	No	Yes	0.9
7	TOF	—	—	Yes	Yes	10.6
8	TOF	BPV,RAA	—	No	No	0.4
9	TOF	AIS	VI	Yes	Yes	12.6
10	TOF	AIS,RAA	—	No	Yes	0.03
11	TOF	RAA	VI,inguinal hernia	No	Yes	5.4
12	TOF/PA	ALSA,RAA	—	Yes	Yes	1.0
13	TOF/PA	RAA	Cleft lip and palate	No	Yes	4.2
14	TOF/PA	NPA	VI,scoliosis,inguinal hernia	No	No	16.4
15	TOF/PA	RAA	—	Yes	Yes	9.6
16	TOF/PA	NPA,RAA	—	Yes	No	1.0
17	IAA/B	—	—	No	Yes	0.01
18	IAA/B	RAA	—	?	Yes	2.4
19	IAA/C	—	—	?	Yes	0.05
20	IAA/B	—	—	No	Yes	1.3
21	IAA/B	ARSA,BAV	Club feet	Yes	No	8.9
22	IAA/B	BAV	—	No	No	10.2
23	IAA/B	AS	—	?	Yes	0.01
24	TA	ALPA	—	?	Yes	2.1
25	TA	RAA	VI	No	Yes	6.3
26	TA	—	—	No	Yes	3.4
27	VSD	BAV	VI	Yes	Yes	0.01
28	VSD	—	Cleft palate	Yes	Yes	19
29	VSD	ARSA	—	No	No	0.3
30	VSD	RAA,CAA, ALSA,RVMB	—	No	No	2.4

*AIS, absent infundibular septum; ALPA, absent left pulmonary artery; ALSA, aberrant left subclavian artery; AS, aortic stenosis; BAV, bicuspid aortic valve; BPV, bicuspid pulmonary valve; CAA, cervial aortic arch; IAA/C, interrupted aortic arch/type C; NPA, nonconfluent pulmonary arteries; RVMB, right ventricular muscle bundles; TE, tracheoesophageal; TOF/PA, tetralogy of Fallot/pulmonary atresia; VI, velopharyngeal insufficiency; Other abbreviations per Table I.

not described in evaluations preceding identification of the chromosome 22 deletion; 3 of these evaluations (patients 4, 22, and 29 in Table II) included an exam by a geneticist.

Pseudomonas pneumonia in a patient with absent pulmonary valve [Johnson et al., 1995a] was the only opportunistic infection identified in patients with deletions. A trend toward hospitalization for respiratory syncytial virus was observed in patients with deletions as compared to patients without deletions (5 of 33 vs. 1 of 37, $P = 0.08$).

There were no sudden, unexplained deaths among the 37 patients without deletions, whereas 4 of 33 patients with deletions (Table II) died suddenly without a cause detected at autopsy ($P < 0.05$): patient 5 was hemodynamically stable until asystole that was unresponsive to resuscitation was observed 12 hours after cardiac surgery, patient 19 could not be resuscitated after sudden asystole in the cardiac catheterization laboratory, and patients 18 and 22 were found dead at home 2 weeks and 10 years, respectively, after apparently successful cardiac surgery.

DISCUSSION

Data from our review indicate that the prevalence of chromosome abnormalities in conotruncal cardiac defects is higher than reported in previous population-based studies that include all congenital cardiac defects. Determining the prevalence of chromosome abnormalities for all congenital heart defects is complicated by increased ascertainment of hemodynamically insignificant defects, especially small ventricular septal defects [Martin et al., 1989; Roguin et al., 1995]. In the Baltimore-Washington Infant Study, 13% of infants with congenital cardiovascular disease have chromosome abnormalities [Ferencz et al., 1989]. If our exclusion criteria are applied to the Baltimore-Washington data, eliminating trisomy 21 patients with atrioventricular canal defects and all trisomy 13 and 18 patients, the prevalence of chromosome abnormalities falls to 5%. Methodological differences limit a direct comparison as our report is a retrospective case series, whereas the Baltimore-Washington study is population based. Our patient base may be enriched due to the tendency to refer patients with multiple malformations to a tertiary center. In addition, our study includes older children rather than restricting ascertainment to infancy. Nevertheless, we believe that our selection of patients with specific cardiac lesions and enhanced sensitivity for deletions with FISH analysis accounts for the higher prevalence of chromosome abnormalities in our study subjects.

TABLE III. Prevalence of Chromosome Abnormalities in Selected Cardiac Defects

	Number	Number of patients tested: FISH and cytogenetic	Number of patients tested: Cytogenetic only	22q11 deletion	Other abnormalities	Total with chromosome abnormality (%)
Tetralogy of Fallot	140	28	7	11	6	17 (12)
Tetralogy of Fallot/pulmonary atresia	19	15	2	5	0	5 (26)
Interruped aortic arch	18	11	1	7	1	8 (44)
Truncus arteriosus	26	11	3	3	0	3 (12)
Absent pulmonary valve[a]	10	9	—	6	0	6 (60)
Double outlet right ventricle	21	11	4	0	1	1 (5)

[a]Patients with deletions previously reported.

Only 36% of our patients with the cardiac defects listed in Table III had FISH analysis. However, similar results for the 22q11 deletion were found in small prospective studies from Italy and Japan. Deletions were detected in 7% (9 of 123) of patients with tetralogy of Fallot and 15% (2 of 13) of those with tetralogy of Fallot/pulmonary atresia [Amati et al., 1995]. Takahashi et al. [1995] found deletions in 3 of 30 patients with tetralogy of Fallot, one of 3 patients with interruption of the aortic arch, and one patient with origin of the right pulmonary artery from the aorta. Although double outlet right ventricle is considered a conotruncal cardiac defect, we and others [Takahashi et al., 1995] have not found 22q11 deletions in patients with this anatomy.

Isolated ventricular septal defects have been reported in patients with DiGeorge and Shprintzen syndromes. A right aortic arch has been reported in 33–50% of these patients [Young et al., 1980; Van Mierop and Kutsche, 1986]. The location of these defects has not been well characterized. All 4 of our patients with del 22(q11) syndrome and isolated ventricular septal defects had surgical confirmation of paramembranous (conoventricular) defects, one also had hypoplasia of the infundibular septum. These data support the concept that the conal region of the developing heart can be disrupted by the 22q11 deletion.

Neither cardiac nor extracardiac manifestations can reliably identify patients with the 22q11 deletion. Twelve (all infants) of 37 patients in our combined series and 2 of 11 patients in a previous prospective study [Amati et al., 1995] had no extracardiac signs of del 22(q11) syndrome identified before deletions were detected. Although data indicate that other arch and conotruncal defects such as right aortic arch, high aortic arch, absent infundibular septum, and aberrant subclavian arteries are more prevalent in tetralogy patients with deletions [Table IV; Momma et al., 1995], none of these are found exclusively in deleted patients. Our series had too few patients with tetralogy/pulmonary atresia to confirm observations that deleted patients with this cardiac defect have a higher incidence of nonconfluent pulmonary arteries and major aortopulmonary collaterals [Momma et al., 1996].

TABLE IV. Frequency of Clinical Findings in Patients With and Without del(22)(q11.21q11.23)

Manifestations	With deletion (%) (n = 33)	Without deletion (%) (n = 37)	*P*
Right aortic arch	17 (52)	11 (30)	0.06
Aberrant subclavian artery	5 (15)	2 (5)	0.2
Syndromal	24 (73)	10 (27)	0.0003
Cleft palate/velopharyngeal incompetence	7 (21)	1 (3)	0.02
Hypocalcemia	8 (24)	0 (0)	0.001

Reports of the spectrum of phenotype associated with del 22(q11) syndrome to date are biased. Ascertainment by congenital heart anomaly has been the primary indication for cytogenetic testing. Evaluation of other relatives in heritable cases has indicated significantly milder phenotypes than in index cases. Although this may reflect the fact that parents of deletion cases would be expected to have milder cardiac phenotypes to have survived into child-bearing years, similar variability has been appreciated in the affected sibs of propositi as well as in affected monozygotic twins [Goodship et al., 1995]. The wide range in phenotype in this disorder points to the need for collaborative studies of large numbers of families segregating the 22q11 deletion to resolve better the phenotypes resulting from this deletion. Given the large numbers of patients ascertained over the past few years, this may be among the most common deletion syndromes in humans [du Montcel et al., 1996].

Ongoing investigations of the 22q11 critical region may allow identification of genes that are important in cardiac development. A gene that encodes a putative transcriptional regulator has been localized to the critical region [Halford et al., 1993]. Cells from the neural crest may play a key role in the pathogenesis of conotruncal cardiac defects [Kirby and Waldo, 1990].

The identification of 5 patients with abnormalities of 8p in our series adds weight to the theory that critical genes for cardiac development are present in this region. Atrioventricular canal and conotruncal lesions are the most frequent cardiac anomalies associated with 8p deletions in our patients and in previous reports; however, other defects described in these patients include valvular pulmonary stenosis, atrial septal defect, ventricular septal defect, double outlet right ventricle, and hypoplastic left heart syndrome [Digilio et al., 1993; Gelb et al., 1991; Hutchinson et al., 1992; Wu et al., 1996]. Patient 3 (Table I) had a complete atrioventricular canal and tetralogy of Fallot. This well-recognized, but infrequent, combination of cardiac defects is associated with trisomy 21 in 35–43% of pa-

tients [Nath et al., 1984; Uretzky et al., 1984]. In our patient with an inverted duplication 8p, the finding of truncus arteriosus (patient 2, Table I) is unusual because typically atrial and ventricular septal defects are associated with 8p duplications [Roskes et al., 1990]. However, it has been demonstrated that inverted 8p duplication patients are deleted of sequences in the 8p23 region [Dill et al., 1987; Guo et al., 1995].

Developmental delay/mental retardation has been a common finding in patients with 8p deletions, occurring in all of our patients and all cases reported by others [Digilio et al., 1993; Hutchinson et al., 1992; Wu et al., 1996]. Others suggest that mental retardation is less severe in the smaller more distal deletions [Hutchinson et al., 1992]. Agenesis of the corpus callosum was found in our patient with an inverted 8p duplication, and partial agenesis was reported in one patient with del(8)(p23) and pulmonary valve stenosis [Hutchinson et al., 1992]. In fact, a presumptive locus for development of the corpus callosum was identified on the basis of patients with trisomy 8 syndrome [Digilio et al., 1994]. Our data also confirm observations that minor facial and genitourinary anomalies are present in patients with chromosome 8p abnormalities [Digilio et al., 1993; Hutchinson et al., 1992].

We conclude that a careful physical examination and cytogenetic analysis with FISH testing for the 22q11 deletion are indicated in patients with absent pulmonary valve, tetralogy of Fallot, tetralogy of Fallot/pulmonary atresia, interrupted aortic arch, and truncus arteriosus. Identification of patients with deletions will facilitate genetic counseling and screening for associated medical conditions such as immune disorders, hypocalcemia, growth delay, learning disabilities, speech disturbances, and renal anomalies [Wilson et al., 1993; Goldberg et al., 1993]. In addition, prophylactic treatment of hypocalcemia in the immediate period after cardiac surgery in these patients may be considered. We speculate that cardiac hypocalcemia may have contributed to the 4 sudden deaths in our patients with 22q11 deletions. Reduced myocardial calcium channel activity was observed in chicks with truncus arteriosus defects secondary to cardiac neural crest ablation [Aiba and Creazzo, 1992]

Addition of our 5 patients with congenital heart defects and 8p abnormalities to those previously reported [Digilio et al., 1993; Gelb et al., 1991; Hutchinson et al., 1992] suggests that this region should be carefully scrutinized in patients with mental retardation and either conotruncal or atrioventricular canal defects.

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